Attorney Docket No. 03/058 LTSBOE
Customer No. 38263

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Frank THEOBALD *et al.*

Application No.: 10/564,932

Filed: January 13, 2006

For: TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING A PRAMIPEXOL ACTIVE AGENT

Group Art Unit: 1614

Examiner: S. M. Rao

Confirmation No.: 4048

APPEAL BRIEF

MS Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Charlotte, North Carolina
October 15, 2010

Dear Sir:

Pursuant to 37 C.F.R. § 41.37, Appellant submits this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Final Office Action of July 6, 2010. A Notice of Appeal was timely filed on October 15, 2010, along with a Petition for one-month Extension of Time.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real parties in interest are LTS Lohmann Therapie-Systeme AG and Boehringer Ingelheim Pharma GMBH & Co. KG, who jointly own the entire right, title and interest in and to the subject application. Assignment to LTS Lohmann Therapie-Systeme AG and Boehringer Ingelheim Pharma GMBH & Co. KG was recorded in the United States Patent and Trademark Office on May 25, 2006, at Reel 017677/0325 and 017677/0355, respectively.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and Assignees are unaware of any prior or pending appeals, interferences or judicial proceedings related to, directly affected by or having a bearing on the subject appeal.

III. STATUS OF THE CLAIMS

Claims 1 through 3, 6 through 12 and 14 through 20, which are all under appeal, stand finally rejected and are found in the Claims Appendix. Claims 4, 5 and 13 have been canceled. No claim is allowed.

IV. STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendment after final rejection has been filed.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present application is directed to self-adhesive transdermal therapeutic systems (TTSs) which are capable of delivering pramipexol continuously over a prolonged period, such as a period of 4 to 7 days. See specification, page 1, lines 4 through 11. The inventive TTSs, incorporating two active-ingredient containing layers formed from pressure sensitive adhesives also addresses the heretofore known lag time associated with pramipexole TTSs, providing an adequate pramipexol flux within 24 hours of application. See specification, page 11, lines 9 through 20 and Fig. 2. The elevated flux rates provided by the claimed invention translates into a much quicker and more prolonged efficacy for the patient.

The inventive TTSs, incorporating a quite elevated pramipexol loading within its outermost polymer layer, further does not require either an adhesive intermediary layer to provide adhesion to the backing layer or a covering plaster. See specification, page 5, lines 4 through 15 and page 12, lines 15 through 17. The absence of such intermediary layer and/or covering plaster translates into a thinner, more comfortable TTS for the wearer.

The subject matter of independent Claim 1 is thus directed to transdermal therapeutic systems for continuous administration of pramipexol that include both first and second pramipexol-containing polymer layers formed from pressure-sensitive adhesive polymer based on carboxyl group-free polyacrylates, in which the first pramipexol-containing polymer layer, disposed directly on the backing layer, includes pramipexol in an elevated proportion of between 25 up to 75 % by weight and the second pramipexol-containing layer, disposed toward the skin, includes pramipexol in a more modest proportion of 2 to 10% by weight, with the resulting TTS providing a flux rate of greater than 5 $\mu g/cm^2$ after only 24 hours after application, with such beneficial flux rate continuing for up to 72 hours after administration. See specification, page 6, lines 8 through 27; page 8, lines 7 through 13; page 10, lines 8 through 13; page 12, lines 15 through 17 and Figure 2.

Independent Claim 18 is directed to transdermal therapeutic systems that include (i) a backing layer, (ii) a first active ingredient-containing polymer layer comprising pramipexol in a proportion of between 10 and less than 75 % by weight and (iii) a second active ingredient-containing polymer layer comprising pramipexol in a proportion of between 2 and 10 % by weight, in which the first and second active ingredient-containing polymer layer are formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion, and the transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration in the absence of an excipient or penetration-promoter and the system has no additional pressure sensitive adhesive top plaster for fixing to the skin. See specification, page 8, lines 7 through 23; page 10, lines 8 through 13; page 12, lines 15 through 17; page 5, lines 10 through 15 and Figure 2.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Claim 1 and dependent Claims 2, 3, 6 through 12, 14 through 17, 19 and 20 stand rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement for the term "directly" within the recitation "a first active ingredient-containing polymer layer disposed **directly** on the backing layer."

B. Claims 1 through 3, 6 through 12, 14 through 16 and 17 through 20 stand rejected under 35 USC § 103, over WO 03/015779, whose United States Equivalent is United States Publication 2004/0247656, which has subsequently matured into United States Patent No. 7,344,733 (Beier) in view of United States Patent No. 5,939,094 (Durif); United States Patent No. 4,769,028 (Hoffmann); United States Patent No. 5,112,842 (Zierenberg) and WO 96/39136 (Patel). Claim 16 stands rejected over Beier, Durif, Zierenber and Patel and further in light of United States Patent No. 5,238,944 (Wick).

VII. ARGUMENT

A. Claim 1 and dependent Claims 2, 3, 6 through 12, 14 through 17, 19 and 20 provide sufficient written description for the term "directly" within the recitation "a first active ingredient-containing polymer layer disposed **directly** on the backing layer."

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." MPEP 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.* 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985)(quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *Id* (citing e.g. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). The subject matter of the claim need not be described literally (i.e. using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement. *Id* Rather, all that is required to satisfy the written description is "reasonable clarity." *Id.*

The specification on page 6, line 35 through page 7, line 3 states that the "active ingredient-containing layer may …be composed of two or more layers which differ in polymer and active ingredient composition." The specification on Page 6, lines 8 through 12 further notes that the active ingredient-containing layer includes a pressure-sensitive adhesive which attaches the TTS to the user's skin.

The specification on page 12, lines 15 through 18, Example 2, discloses the production of a transdermal therapeutic system "consisting of backing layer and two active ingredient-containing layers." Example 2 indicates that the first active ingredient-containing layer, noted as the reservoir layer, includes 40 % by weight pramipexol and 60 % by weight Durotak 2287, while the second active ingredient-containing layer, noted as the pressure-sensitive adhesive layer, includes 3 % by weight pramipexol and 97 % by weight Durotak 2287, per Application-as-filed, Page 12, lines 17 through 24. The specification on page 12, lines 24 through 28 then states that the resulting laminate of Example 2 consists of a "backing layer, reservoir layer and a pressure-sensitive adhesive layer."

The specification thus conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the recited first active ingredient-containing polymer layer disposed **directly** on the backing layer." The exemplary construction of Example 2 "consists of," i.e. is limited to, a total of three layers: a backing layer, a reservoir layer and a pressure-sensitive adhesive layer." One skilled in the art clearly understands that the "backing" layer constitutes an outermost layer of the TTS of Example 2, particularly the outer layer facing away from the wearer. One skilled in the art likewise understands that the pressure-sensitive adhesive layer of Example 2 constitutes the opposing outermost layer of the TTS, particularly the outer layer facing toward (and ultimately adhered to) the wearer, as evidenced within the specification. One skilled in the art would further understand that the remaining reservoir layer would be disposed between the backing layer and the pressure sensitive layer, as evidenced by Hoffmann at Column 2, lines 4 through 21 (describing a "reservoir layer" adjacent to a "backing layer."), as well as within the specification on page 6, line 35 through page 7, line 3 stating that the active ingredient layer active ingredient-containing layer may include two or more layers.

Consequently, as the "closed" language describing Example 2 limits it to a total of three layers and the backing layer and pressure-sensitive adhesive layer form the outermost layers, the innermost layer (i.e. the first active ingredient-containing polymer layer or reservoir layer) is, by definition, disposed between them. As no additional layers may be included within the

exemplary TTS construction of Example 2 due to the closed phrase "consisting of", the first active ingredient-containing polymer layer must further be directly disposed upon both the outer layers, hence it is directly disposed upon the backing layer. To conclude differently would require the incorporation of a fourth layer, which is clearly excluded by the "closed" language describing Example 2. Applicants have thus conveyed with more than reasonable clarity to those skilled in the art that, as of the filing date sought, they were in possession of the claimed invention.

The application-as-filed thus provides sufficient written description for the term "directly" within the recitation "a first active ingredient-containing polymer layer is disposed **directly** on the backing layer," and reversal of the Examiner's rejection of Claim 1 and dependent Claims 2, 3, 6 through 12, 14 through 17, 19 and 20 is respectfully requested.

B. Claims 1 through 3, 6 through 12, 14 through 16 and 17 through 20 are patentable in light of Beier, Durif, Hoffmann, Zierenberg and Patel. Claim 16 is likewise patentable in further light of Wick.

1. Claims 1 through 3, 6 through 12, 14 through 16 and 17 through 20 are patentable in light of Beier, Durif, Hoffmann, Zierenberg and Patel, because, inter alia, their combination teaches away from the claimed invention and further yields more than predictable results.

An obviousness rejection under 35 U.S.C. § 103 is appropriate only when the differences between the claimed invention and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999); 35 U.S.C. § 103 (a). The ultimate determination of whether an invention would have been obvious is a legal conclusion based on underlying factual inquiries including : (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) any objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 – 18, 148 USPQ 459, 467 (1966).

The USPTO has issued guidelines to its Examiner's pointing out that the *KSR* decision (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734, 82 USPQ2d 1385, 1392 (2007)) reaffirmed the analytical framework for obviousness that was presented in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). *Fed. Register*, Vol. 75, No. 169, Sept. 1, 2010, p 53643 – 53647. The guidelines note that Examiners must provide a reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention. *Id* at p 53645.

The clear articulation of the reason(s) why the claimed invention would have been obvious is key to supporting any rejection under 35 USC § 103. Under KSR, the analysis supporting an obviousness rejection should be made explicit. KSR said such rejections "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness," quoting *In re Kahn*, 441 F.3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006).

The guidelines further encourage Examiners to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id* at p 53646 (citing KSR, 550 U.S. at 401). Combinations of elements based upon illogical modifications that ignore the teachings of the prior art have particularly been held to be indicative of nonobviousness. *Crocs, Inc. v. U.S. International Trade Commission*, 598 F.3d 1294 (Fed. Cir. 2010)

The guidelines also caution that "merely pointing to the presence of all claim elements in the prior art is not a complete statement of a rejection for obviousness. In accordance with MPEP § 2143 A(3), a proper rejection based on the rationale that the claimed invention is a combination of prior art elements also includes a finding that results flowing from the combination would have been predictable to a person of ordinary skill in the art." Fed. Register at 53647 citing *Crocs, Inc. v. U.S. International Trade Commission*, 598 F.3d 1294 (Fed. Cir. 2010).

In the instant case, the first active ingredient-containing polymer layer comprising the claimed elevated amounts of pramipexol within carboxyl group-free polyacrylate pressure-sensitive adhesive disposed directly on a backing layer, as recited in independent Claim 1, is not in the prior art and is not a predictable result flowing from the combined references.

Beier merely discloses that moderate amounts of pramipexol may be incorporated into solvent based acrylic matrices made of polyacrylates that contain acrylic acid and the like. The prior art reference Hoffman teaches that elevated concentrations of active ingredients, such as a 10% loading, within polymer matrices cause a loss of adhesion, thus requiring an additional adhesive layer adjacent to the backing layer. Zierenberg suggests that emulsion polymerized polymers, i.e. water based polymers, are suitable for more elevated loadings of pramipexol and that such water based polymers do not exhibit orthostatic side effects. Consequently, the Examiner's statement within the outstanding Office Action on Page 16, first full paragraph, that an ordinary artisan would be imbued with at least a reasonable expectation of success based upon the prior art is merely a conclusory statement. The Examiner has instead indulged in an impermissible hindsight analysis by picking and choosing elements from the prior art while using the instant application as a guide. The claimed invention, incorporating extremely elevated amounts of pramipexol within a carboxyl group-free polyacrylate layer disposed directly upon a backing layer clearly would not have been predictable to a person of ordinary skill in the art, based upon the express teachings of the cited prior art.

Similarly, inventive embodiments in which the first active ingredient-containing polymer layer comprises up to 75 % pramipexol within carboxyl group-free polyacrylate pressure-sensitive adhesive and the transdermal therapeutic system includes no excipient, penetration-promoter or top plaster, as claimed in independent Claim 18, is not in the prior art. The prior art reference Beier clearly teaches with particularity the incorporation of penetration enhancers for pramipexol in an acrylic matrices, while Zierenberg teaches the use of a top plaster in combination with pramipexol formulations. None of the remaining cited references cure this deficiency.

The primary reference, Beier, expressly teaches a moderate amount of pramipexole within a single layered matrix that further includes a penetration enhancer. Zierenberg merely teaches the incorporation of higher amounts of pramixpexole in single layered pramipexole TTSs formed from water-based polyacrylate that further include a covering plaster. The remainder of the references are not directed to pramipexole. Durif merely incorporates apomorphine in amounts of up to 10 % into a silicone adhesive that further contains a penetration-enhancer. Hoffmann incorporates any of a laundry list of active ingredients into silicon rubber or the like. Hoffmann does, however, expressly teach that TTSs incorporating elevated quantities of active ingredients within an adhesive layer, such as an exemplary loading of about 10 %, require an additional adhesive intermediary layer between the adhesive layer and the backing layer. Patel merely discloses ropinirole in undisclosed amounts within a water-based matrix sufficient for once-a-day application.

Accordingly, the cited references, considered either alone or in combination, simply do not teach or suggest the inventive multi-layered TTSs containing an active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer that contains between 25 to 75 % pramipexol disposed directly on a backing layer, much less that such a TTS would provide a flux rate greater than 5 $\mu g/cm^2$ hr up to 72 hours after administration, as recited in independent Claim 1.

And the combination most certainly does not teach or suggest such TTSs that do not include penetration enhancer or a covering plaster, as recited in independent Claim 18.

The combined prior art, considered in view of common knowledge at the time of the invention, is required to at least suggest the claimed invention in its entirety, in contrast to the Examiner's apparent urgings to the contrary in the outstanding Office Action on Page 20, first full paragraph, penultimate sentence. As indicated, above, this burden has clearly not been met.

Beier initally teaches that the pramipexol within the cited Zierenberg patch crystallizes out, and thus has poor storage stability. (US 773, Col. 1, lines 57 – 65). Beier is thus generally directed to TTSs providing improved shelf stability that include a maximum of 15 % by weight active ingredient. (US 733, Col. 2, line 66 - Col. 3, line 2 and Col. 2, lines 19 - 20). Beier provides a generic laundry list of suitable pressure sensitive adhesives, including polyurethane. (US 733, Col. 3, lines 23 – 26). In contrast to the recited carboxyl group-free polyacrylates, Beier instead expressly teaches acrylic acid and methacrylic acid as suitable monomers within its matrix polymer. (US 733, Col. 3, lines 50 – 52). Beier merely generically notes that its systems may include one or more matrix layers. (US 733, Col. 2, lines 40 – 45). Beier notes that permeation enhancers may be included "where applicable." (US 733, Col. 2, lines 40 – 45). The working examples of Beier incorporate permeation enhancer, i.e. Copherol®, in conjunction with acrylic-based matrix layers; however. (US 733, Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)). The working examples of Beier further teach the incorporation of 2.5 to 3 weight % active ingredient within a single layer of acrylic-based matrix. (US 733, Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)).

The secondary references do not overcome the deficiencies in Beier.

Zierenberg, the only remaining reference directed to pramipexol, is drawn to single-active-ingredient-layer TTSs that further include a covering plaster which "secure[s] the system to the skin." (US 842, Col. 2, lines 11 – 15). Zierenberg broadly notes that its active ingredient layer may be formed from "emulsion polymerized polyacrylate," i.e. a water-based polyacrylate, preferably Eudragit® NE 30 D (US 842, Col. 1, line 64 – Col. 2, line 2 and Col. 2, lines 18 – 20). As noted in the specification on Page 3, line 35 through Page 4, line 1, Eudragit® NE 30 D is not a pressure sensitive adhesive. Consequently, the backing layer is formed as a "covering plaster" so that it may secure the system to the skin. (US 842, Col. 2, lines 11 – 15). The working examples of Zierenberg include 9 wt % active substance within a single layer. (US 842, Col. 2, lines 53 – 62). Zierenberg curiously provides concentration data beginning on the 3rd day and ending on the 4th day following application. (US 842, Col. 3, lines 2 – 12). In vitro investigations on samples of the TTSs indicate that about 70 % of the amount of active ingredient

had been delivered after only 4 days and that only about a further 10% of the amount of active ingredient originally present in the reservoir can be released in the subsequent three days. (US 842, Figure 1, as interpreted in the Application-as-filed on Page 4, lines 9 – 14).

The remaining secondary references are directed to active ingredients having an altogether different chemical constitution from the recited pramipexol.

Durif is directed to apomorphine, an active ingredient having an altogether different chemical constitution from the recited pramipexol. (US 094, Col. 2, lines 41 – 44). The apomorphine of Durif may be administered as a water soluble gel composition or as a transdermal patch. (US 094, Col. 2, lines 44 – 50). The water soluble gel includes up to 40 % water, ensuring effective topical delivery and bioavailability. (US 094, Col. 2, lines 56 – 60). In the alternative, the apomorphine of Durif may be delivered from discoid dosage form from a silicone-adhesive matrix containing a permeation enhancer. (US 094, Col. 3, lines 39 – 42; Col. 8, lines 1 – 16; Col. 9, lines 31 – 41 and Col. 12, lines 41 - 44). The apomorphine may be present within the discoid matrix layer in amounts of up to 10 % by weight. (US 094, Col. 8, lines 42 – 44). By comparison, the permeation enhancer, which includes butylated hydroxytoluene and the like, may be present in amounts of up to about 30 % by weight. (US 094, Col. 3, lines 44 – 51).

Evidencing conventional wisdom, the permeation enhancer is said to "increase[s] the permeability of the treated area of skin to apomophine to a magnitude such that sufficient apomorphine is absorbed to provide a therapeutically effective level of apomorphine in the bloodstream." (Col. 5, lines 8 – 12). Durif goes on to teach that "the permeation enhancer modulates the rate at which the skin absorbs the apomorphine." (Col. 5, lines 15 – 20). US 094 generically indicates that its multi-layered discoid patches contain both apomorphine and penetration enhancer, which may "differ in amount in each layer." (Col. 8, lines 63 – 65). The working examples indicate that the transdermal patches of US 094 deliver 100 % of the apomorphine within 3 hours or less. (Col. 21, lines 52 - 58).

Hoffmann generically discloses medical bandages containing therapeutically active agents in up to 12 layers. (US 028, Col. 2, lines 4 – 21 and Col. 6, lines 13 - 17). Suitable therapeutically active agents include any of a laundry list of medicaments, including antibiotics, hormones, anti-migraine agents and the like. (US 028, Col. 4, lines 16 – 26). Hoffmann does not teach a suitable range of amounts of active agent within its reservoir layers, but does expressly note that elevated quantities of active ingredients may cause the layer to lose its adhesive power, and thus require an additional adhesive intermediary layer. (US 028, Col. 3, lines 15 – 20 and Col. 4, lines 27 - 33). The therapeutically active agent is contained in a "polymer matrix," which Hoffmann goes on to define as a "base polymer and usual additives." (US 028, Col. 3, lines 47 – 52). Suitable polymer bases include caoutchouc, a natural rubber, and polyurethane. (US 028, Col. 3, lines 54 – 58). The working examples are directed to nitroglycerine bandages worn for up to 26 hours. (US 028, Col. 9, lines 5 – 23). The working examples of Hoffmann contain about 10 % active ingredient within the outermost reservoir layer and further include an adhesive intermediary layer. (US 028, Col. 8, lines 6 – 28 and Col. 10, lines 30 – 48).

Patel is merely directed to the use of ropinirole in free base form as an active ingredient in either membrane-based or maxtrix-based transdermal devices. (WO 136, Page 1, line 34 – Page 2, line 5 and Page 2, lines 15 - 21). Patel is curiously silent as to the amount of ropinirole free base within its formulations, other than to note that sufficient ropinirole is to be provided for a 24 hour period, as it is intended for once-a-day application. (WO 136, Page 3, lines 24 – 26). The working examples of Patel include a single drug-containing layer formed from either a saline/propylene glycol "vehicle" within the membrane-based TTS or a hydrogel within the matrix-based TTS. (WO 136, Page 4, lines 14 – 36). The hydrogel of Patel is formed from polyvinyl alcohol ("PVA") and polyvinylpyrrolidone ("PVP"). (WO 136, Page 4, lines 33 – 34). The hydrogel further includes glycerin as an excipient. (WO 136, Page 4, line 34). The working examples include either a silicone adhesive or undisclosed adhesive. (WO 136, Page 4, lines 14 – 36). Patel further teaches that a penetration enhancer may be added. (WO 136, Col. 2, lines 24 – 25).

Patel merely provides extended penetration data based upon the percutaneous penetration of the saturated saline or saline/propylene glycol vehicle alone. (WO 136, Page 5, lines 1 – 21). Patel does not teach or suggest that its TTSs provide such extended release, but instead tests suspensions of ropinirole to determine its "relative potential" in transdermal systems. (WO 136, Page 5, lines 3 – 5). Patel merely note that, based on its initial solution study, a sufficient quantity of ropinirole free based was found to penetrate the skin for a 24 hour period and a patch delivering a sufficient quantity of ropinirole could "potentially" be formed. (WO 136, Page 6, lines 7 – 9).

Applicants respectfully submit that here would have been no motivation to have combined Beier, Zierenberg, Durif, Hoffmann, and Patel. As noted in Applicants' Amendment of March 2, 2010, one skilled in the art would not transfer the teachings from other active ingredients, e.g. apomorphine (Durif), anti-migraine agents and the like (Hoffmann), ropinirole (Patel), to pramipexol, as these active ingredients have a significantly different chemical constitution and associated physical properties.

However, even if Applicants had combined the cited references (which they did not), the invention of Claims 1 through 3, 6 through 12, 14 through 16 and 17 through 20 would not have resulted.

As noted above, the cited references, considered either alone or in combination, simply do not teach or suggest the inventive TTSs containing a first active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer that contains from 25 to 75 % pramipexol disposed directly on a backing layer, much less such a TTS providing a flux rate greater than 5 $\mu g/cm^2$ hr up to 72 hours after administration, as recited in Claim 1. Instead, the only teaching as to highly loaded adhesive matrices is that extreme active ingredient loadings are highly detrimental to the structural integrity of TTSs and thus requires an intermediate adhesive layer. In that regard, the prior art Hoffmann additionally teaches that a 10 % loading of active ingredient would require an intermediate adhesive layer.

In fact, none of the cited references even teaches or suggest that a first active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer could even be loaded with from 25 to 75 % pramipexol. Beier, who generically teaches acrylics, including acrylics containing acrylic acid, i.e. a carboxylic acid, incorporates a maximum of 15 % pramipexol. Zierenberg includes a higher loading of pramipexol than Beier; however, Zierenberg suggests that a non-adhesive emulsion polymerized polyacrylate promotes such elevated loading. The remainder of the cited references are not directed to pramipexol.

The combined prior art thus can not teach or suggest transdermal therapeutic systems incorporating first and second active ingredient-containing polymer layers formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates containing the recited amounts of pramipexol that do not include water or an aqueous dispersion would provide such advantageous pramipexol flux rates in the absence of excipients or penetration-promoters and further without a top plaster, as recited in Claim 18.

Beier, expressly including a penetration promoter for pramipexol within a polyacrylate matrix, clearly suggests that permeation enhancers are "applicable" for polyacrylates, in contrast to the Examiner's urgings in the outstanding Office Action on Page 22, first and second full sentences. Durif likewise indicates that its discoid patches contain penetration enhancer. Hoffmann teaches use of the "usual additives" in dispensing antibiotics and the like from natural rubber. Patel expressly teaches active ingredient within a hydrogel or saline solution. Zierenberg is directed to TTSs incorporating an emulsion polymerized non-adhesive matrix requiring a top plaster.

Accordingly, Applicants respectfully submit that the present invention as defined within Claims 1 and 18 and all claims dependent thereon is patentable in light of each of Beier, Durif, Hoffmann, Zierenberg and Patel, considered either alone or in any combination.

B. Claim 16 is likewise patentable in light of Beier, Durif, Zierenberg, Patel, and Wick.

Wick is directed to formulations for the topical or transdermal delivery of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, an anti-viral, using isostearic and/or oleic fatty acid. (US 944, Col. 1, lines 49 – 63 and Col. 2, lines 1 - 4). The fatty acid may be included in amounts of up to 45 % by weight. (US 944, Col. 3, lines 49 – 52). The 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine may be present in amounts of up to 9 % by weight. (US 944, Col. 3, lines 43 – 46). Wick indicates that suitable adhesives include 4 to 9 % acrylic acid or methacrylic acid reinforcing monomer. (US 944, Col. 6, lines 23 – 24 and lines 33 - 34). Wick is merely directed to single-layered transdermal devices. (US 944, Col. 16, lines 45 – 65). Wick further indicates that skin penetration enhancers may be incorporated, in amounts of up to 25 %. (US 944, Col. 2, lines 48 – 51 and Col. 7, lines 23 - 38).

Regardless of any general teachings Wick may arguably contain regarding adhesive copolymers, it does not teach or suggest the claimed invention. Wick instead merely discloses the incorporation of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine in a maximum amount of 9 % by weight within an adhesive that may include acid groups.

Applicants respectfully submit that there likewise would have been no motivation to have combined Beier, Durif, Zierenberg, Patel and Wick. However, even if Applicants had combined the foregoing references (which they did not), the claimed invention would not have resulted.

None of the cited references, considered either alone or in combination, teach or suggest the inventive TTSs containing a first active ingredient layer formed from carboxyl-group-free polyacrylate pressure-sensitive adhesive polymer that contains from 25 to 75 % pramipexol disposed directly on a backing layer, much less such a TTS providing a flux rate greater than 5 $\mu g/cm^2$ hr up to 72 hours after administration, as recited in Claim 16.

Instead, the only teaching as to highly loaded adhesive matrices is that extreme active ingredient loadings, such as a loading of at least 10 %, are highly detrimental to the structural integrity of TTSs and thus require an intermediate adhesive layer. Wick, directed to the incorporation of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine in a maximum amount of 9 % by weight within adhesive that may include acid groups, does not cure this deficiency.

Accordingly, Claim 16 is likewise patentable in light of Beier, Durif, Zierenberg, Patel and Wick, considered either alone or in any combination.

VIII. CONCLUSION

For the reasons argued above, the reversal of the rejection of Claims 1, through 3, 6 through 12, 14 through 17, 19 and 20 under 35 USC 112, first paragraph, is respectfully requested.

For the reasons argued above, the reversal of the rejection of Claims 1 through 3, 6 through 12, 14 through 20 under 35 USC § 103 is also respectfully requested.

Respectfully submitted,

Cathy Moore

Cathy R. Moore
Reg. No. 45,764

ProPat, L.L.C.
425-C South Sharon Amity Road
Charlotte, NC 28211-2841
Telephone: (704) 365-4881
Fax: (704) 365-4851
Customer No. 38263

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being transmitted to the United States Patent and Trademark Office PAIR Webpage via the electronic filing system in accordance with 37 CFR § 1.6(a)(4) on October 15, 2010.

Claire Wygand Ms. Claire Wygand

CLAIMS APPENDIX

1. A transdermal therapeutic system for continuous administration of pramipexol comprising

a backing layer and a first active ingredient-containing polymer layer disposed directly on the backing layer which comprises the active ingredient pramipexol, wherein the first active ingredient-containing polymer layer comprises at least one pressure-sensitive adhesive polymer selected from carboxyl group-free polyacrylates, where the active ingredient pramipexol is present in said first active ingredient-containing polymer layer in a proportion of between 25 to less than 75 % by weight

and said transdermal therapeutic system includes a second active ingredient-containing polymer layer disposed on the first active ingredient-containing polymer layer, said second active ingredient-containing polymer layer comprising at least one pressure-sensitive adhesive polymer selected from carboxyl group-free polyacrylates, where the active ingredient pramipexol is present in said second active ingredient-containing polymer layer in a proportion of between 2 and 10 % by weight, whereby the transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration.

2. The transdermal therapeutic system as claimed in claim 1, which further comprises at least one element selected from the group consisting of a pressure-sensitive adhesive layer, a membrane which controls the rate of release of pramipexol, an active ingredient-containing layer or a supporting layer.

3. The transdermal therapeutic system as claimed in claim 1, wherein the pressure-sensitive adhesive polymer is a carboxyl group-free polyacrylate which can be prepared by polymerization of a monomer mixture of at least one acrylic ester or methacrylic ester with linear, branched or cyclic aliphatic C_1-C_{12} substituents without other functional groups, and at least one hydroxyl group-containing acrylic ester or one hydroxyl group-containing methacrylic ester in a proportion by weight of less than 10%.

4. (Canceled)

5. (Canceled)

6. The transdermal therapeutic system as claimed in claim 3, wherein the monomer mixture additionally comprises vinyl acetate in a proportion by weight of less than 50 %.

7. The transdermal therapeutic system as claimed in claim 1, wherein the active ingredient pramipexol is present in the active ingredient-containing polymer layer in dissolved, emulsified and/or dispersed form.

8. The transdermal therapeutic system as claimed in claim 1, wherein the active ingredient pramipexol is present as *S*-(-) enantiomer, *R*-(+) enantiomer or racemic mixture of these two enantiomers in the active ingredient-containing polymer layer.

9. The transdermal therapeutic system as claimed in claim 1, wherein the active ingredient pramipexol is present as a free base, hydrate, solvate and/or pharmaceutically acceptable salt in the active ingredient-containing polymer layer.

10. The transdermal therapeutic system as claimed in claim 1, wherein the active ingredient pramipexol is present as *S*-(-) enantiomer in the form of a free base in the active ingredient-containing polymer layer.

11. The transdermal therapeutic system as claimed in claim 1, wherein said transdermal therapeutic system delivers the active ingredient pramipexol continuously to a patient's skin over a period of from 4 to 7 days.

12. The transdermal therapeutic system as claimed in claim 1, which is able to release the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ h over the period between 24 hours after administration to 168 h after administration.

13. (Canceled)

14. The transdermal therapeutic system as claimed in claim 1, wherein the active ingredient pramipexol is present in said first active ingredient-containing polymer layer in a proportion of between 25 and 40 % by weight.

15. The transdermal therapeutic system as claimed in claim 1, wherein the daily delivery rate of pramipexol is between 0.1-10 mg.

16. The transdermal therapeutic system as claimed in claim 3, wherein the pressure-sensitive adhesive monomer mixture additionally comprises vinyl acetate in a proportion of less than 25% by weight and the pressure-sensitive adhesive does not comprise water or an aqueous dispersion.

17. The transdermal therapeutic system as claimed in claim 1, wherein the daily delivery rate of pramipexol is between 0.5 to 4.5 mg.

18. A transdermal therapeutic system for continuous administration of pramipexol comprising (i) a backing layer, (ii) a first active ingredient-containing polymer layer comprising pramipexol in a proportion of between 10 and less than 75 % by weight and (iii) a second active ingredient-containing polymer layer comprising pramipexol in a proportion of between 2 and 10 % by weight,

wherein the first and second active ingredient-containing polymer layer comprise pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion,

and said transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration in the absence of an excipient or penetration-promoter and said system has no additional pressure sensitive adhesive top plaster for fixing to the skin.

19. The transdermal therapeutic system as claimed in Claim 1, wherein the first and second active ingredient-containing polymer layers comprise pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion, and the transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration in the absence of a penetration-promoter, and said system has no additional pressure sensitive adhesive top plaster for fixing to the skin.

20. The transdermal therapeutic system as claimed in claim 19, wherein the first and second active ingredient-containing polymer layers consist of pramipexol and carboxyl group-free polyacrylate pressure-sensitive adhesive.

EVIDENCE APPENDIX

No evidence is being submitted with this Appeal Brief.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings and therefore no final decisions have been rendered in related proceedings.